REMARKS

Amendments in the specification

Paragraph numbers below refer to the Substitute Specification (clean copy) submitted on 3 April 2008.

The specification is amended herein to add the title "CROSS-REFERENCE TO RELATED APPLICATIONS" before paragraph **[0001]**.

Paragraph **[0001]** is amended herein to add incorporation by reference language for the listed priority documents, and refer to related U.S. Serial No. 10/523,908 filed on 29 July 2003.

No new matter is introduced by the present amendment.

Amendments in the claims

Claims 1–16, 18 and 20–31 are pending in the present application. Claims 17 and 19 were cancelled by an earlier amendment. Claims 26–31 are added by the present amendment.

Claims 14–16 are amended for enhanced clarity by reciting in each case a structural limitation, namely the amount of rotigotine present in the TTS effective to provide the specified result.

New Claims 26–28 are drawn to a TTS containing rotigotine in an amount effective for treatment of a disease associated with a dopamine-metabolism disorder (Claim 26), for example Parkinson's disease (Claim 27) or restless leg syndrome (Claim 28). Support for a "therapeutically effective" amount of rotigotine is found in the specification as filed, for example at p. 17, last paragraph; and support for the recited diseases is found in the specification as filed, at least at p. 21, first paragraph.

New Claims 29–31 are drawn to a method for treating a disease associated with a dopamine-metabolism disorder (Claim 29), for example Parkinson's disease (Claim 30) or restless leg syndrome (Claim 31), comprising applying a TTS of Claim 1 to skin of a patient in need thereof. Support for such a method is found in the specification as filed, for example at p. 21, second paragraph.

The present amendments and new claims are submitted in view of the Request for Withdrawal of Finality filed 18 May 2009 and the remarks presented in the Statement of Substance of Interview found below.

No new matter is added, and no change in inventorship is believed to occur, as a result of any amendment herein.

STATEMENT OF SUBSTANCE OF INTERVIEWS

The Interview Summary prepared by the Examiner in the above-referenced case and mailed on 19 May 2009 is not in complete accordance with the understanding of Applicant's representatives. Applicant respectfully notes as follows.

Applicant's representatives William Ziehler and Leanne Rakers believe that the Examiner's suggestion was not to submit a full response to the final rejection prior to a determination by the Office on the question of finality. Instead, these representatives understood (and have acted on this understanding) that the Examiner's suggestion was to submit in writing a request for withdrawal of finality; if such request were approved a new non-final action would be issued, and if denied, Applicant's recourse would be (within the statutory period for response to the 19 March 2009 Office Action) to file notice of appeal or request for continued examination (RCE).

As correctly recorded in the Examiner's Interview Summary, Applicant's representatives observed that a full response within the two-month period (*i.e.*, not later than 19 May 2009) would not be possible because of the time required for review in Germany.

Applicant's representative William Ziehler subsequently submitted a Request for Withdrawal of Finality on 18 May 2009. The request identifies that independent Claim 18, which was not amended in the reply of 22 December 2008, expressly includes melting components of the cement matrix, which includes rotigotine. This is in contradistinction to the Examiner's Response to Arguments on page 7, lines 1-2 of the Office Action dated 19 March 2009, where it is alleged the method claims do not require melting the active agent. Thus, the Examiner's basis for applying final status is incorrect.

Applicant's representative William Ziehler spoke again with the Examiner on 18 September 2009 regarding the request to withdraw finality. The Examiner indicated that since the method of Claim 18 recites a temperature range of 70°C and 200°C, the claim does not necessarily require melting rotigotine, where the melting point of rotigotine is about 75°C as noted on page 19, paragraph [0115] of the original specification. However, the Examiner's position still does not account for dependent Claim 24, as provided before the final Office

Action, which recites that the melting of Claim 18 takes place at a temperature between 120°C and 160°C, which is well above the melting temperature of rotigotine (about 75°C). Thus, the Examiner's allegation that the method claims do not require melting the active agent is incorrect.

Accordingly, Applicant respectfully maintains that the finality of the Office Action dated 19 March 2009 is premature.

RESPONSE TO OFFICE ACTION DATED 19 MARCH 2009

1. Obviousness-type double patenting

Claims 1–16, 18 and 20–25 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–59 of copending application Serial No. 10/523,908.

The rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent.

2. Rejection under 35 U.S.C. §103(a) over Chen in view of Metman and Loper

Claims 1–3, 6–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,807,570 ("Chen"), in view of Metman *et al.* (2001) Clinical Neuropharmacology 24:163–169 ("Metman") and U.S. Patent No. 4,880,633 ("Loper"). This rejection is respectfully traversed.

The present claims are not obvious over the combination of Chen, Metman, and Loper as the references fail to provide for all of the claimed features. To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); and *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). In the case of Claim 1, the structure resulting from the process of dispersing, melting, and dissolving rotigotine in the hot-melt adhesive is absent. In the case of Claim 18, the references fail to provide for melting and homogenizing components of the cement matrix, solvent-free, where the cement matrix contains rotigotine. In the case of Claim 20, the references fail to provide for pre-melting and

homogenizing components of the cement matrix, solvent-free, and introducing rotigotine into the pre-melted matrix. Details and shortcomings of the Chen, Metman, and Loper disclosures are presented in Applicant's amendment filed 22 December 2008 and are further illustrated below.

First, all the features of Claim 1 must be considered against the combination of Chen, Metman, and Loper. In particular, the transdermal therapeutic system (TTS) of Claim 1 is formed using a process that imparts a structure unattainable by the cited references: "the cement matrix comprises a hot-meltable adhesive in which the active substance is dispersed and melted using a hot-melt process," the active substance being rotigotine. As claimed, the rotigotine is dispersed and melted, whereas nowhere in the combination of Chen, Metman, and Loper is there any disclosure or suggestion with respect to dispersing and melting an active substance.

Structure implied by processing should be considered when assessing the patentability of product-by-process claims over the prior art where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (holding "interbonded by interfusion" to limit structure of the claimed composite and noting that terms such as "welded," "intermixed," "ground in place," "press fitted," and "etched" are capable of construction as structural limitations.). In the present case, a "cement matrix compris[ing] a hot-meltable adhesive in which the active substance is dispersed and melted using a hot-melt process" makes the presently claimed TTS structurally distinguishable from anything found in Chen, Metman, and Loper, as none of the references melt the active substance, and in particular, the "hot-melt deposition, extrusion and the like" of Loper employs a solution of drug and matrix material, where solvent is removed by drying (col. 8, lines 21–23). As the drug is in solution with solvent, the drug cannot be said to be "melted". Furthermore, no indication is given by Loper that "hot-melt deposition, extrusion and the like" is carried out at a temperature above the melting point of the drug, which would presumably have to be less than the boiling point of the solvent employed in Loper.

Applicant submits that dispersion of melted rotigotine in melted adhesive, as per Claim 1, blends two molten materials resulting in a structurally distinct material from a

solution of dissolved drug where solvent is removed by drying, as per Loper's contribution to the combination. As evidence, Applicant refers the Examiner to page 2, lines 12-19 of the present specification which illustrates drawbacks of solvent-based delivery systems. For example:

> [A]s the solvent is removed during the production process, the relative concentration of the active substance increases, which can lead to an oversaturation of the matrix and to an undesirable formation of crystals. This again places a limit on the maximum amount of the active substance that can be worked into the matrix. Yet a low-level infusion of the active substance limits the release capacity of the matrix per unit of time and/or its functional lifespan due to a premature depletion of the active substance.
> (Specification page 2, lines 12-19)

Therefore, the TTS of Claim 1 is structurally distinct from a combination transdermal delivery system based on the cited references, where crystallization of the drug upon solvent removal may be expected.

The present specification further illustrates differences between solvent-based systems and hot-melt systems on page 11, lines 1-15. For example, solvent-based silicone adhesives can accept at the most 15 weight % of active-substance, while adhesive matrices of hot-melt TTSs can accept significantly greater amounts of rotigotine; e.g., up to 40 weight %. Loper's use of a solution of drug and matrix material, where solvent is removed by drying, would therefore limit the weight % amount of active-substance in comparison to the presently claimed TTSs made using the hot melt process. See specification page 11, lines 12-15 and claim 8 that provide TTS embodiments having greater than 15 weight % active-substance (e.g., 20-40% rotigotine).

Since the combination of Chen, Metman, and Loper fails to provide for features of the present process (i.e., melting rotigotine) the combination cannot produce the structure of the presently claimed TTS or provide the amount active-substance loading. Accordingly, Claims 1-16 are not *prima facie* obvious.

Second, the present rejection has not considered all the features of Claim 18 against the combination of Chen, Metman, and Loper. In particular, Claim 18 recites "[a] method for preparing a TTS that comprises a rotigotine-containing cement matrix, the method comprising **melting** and homogenizing components of the cement matrix, **solvent-free**, in an extruder at a

temperature between 70°C and 200°C prior to lamination of the components" (emphasis added). Hence, the claim expressly provides for melting the rotigotine-containing cement matrix in contradistinction to the Examiner's Response to Arguments, Office Action dated March 19, 2009, page 7, lines 1-2. Applicants submit that the Examiner has mischaracterized the claims and that the combination of Chen, Metman, and Loper fails to provide for melting the active agent. Moreover, the present claim language expressly recites that the components of the cement matrix are melted and homogenized solvent-free. Loper's contribution to the combined process of "hot-melt deposition, extrusion and the like" notably uses solvent, which is antithetical to the present claims. As such, Claims 18 and 24 are not *prima facie* obvious.

Third, with respect to Claims 20-23 and 25, the combination of Chen, Metman, and Loper lacks any disclosure relating to "**pre-melting** and homogenizing components of the cement matrix other than the rotigotine, **solvent-free**, and introducing rotigotine at a temperature between 70°C and 200°C, into the pre-melted cement matrix" (emphasis added). In this case, the cement matrix components are pre-melted and rotigotine is introduced thereafter. The process provided by Loper's contribution to the reference combination (e.g.., "hot-melt deposition, extrusion and the like") is silent with respect to any such details. Nowhere in the collective disclosures of Chen, Metman, and Loper is the "reservoir matrix material" pre-melted then mixed with drug. For example, the limit of Loper's contribution is that "[a] solution of drug and reservoir matrix material is coated onto an impermeable backing . . . solvent is removed . . . [where] the reservoir matrix may be coated onto the backing material using other techniques such is [sic] hot melt deposition, extrusion and the like." Loper col. 8, lines 20-29. Nothing indicates any pre-melting occurs in the reference combination. Likewise, the present claims expressly provide pre-melting and homogenizing components solvent-free, which precludes any collective solvent-based "hot-melt deposition, extrusion and the like" process based on the combination of Chen, Metman, and Loper. Claims 20-23 and 25 are consequently not *prima facie* obvious.

Where the combined references are missing claimed features, a case of obviousness requires an apparent reason, based either on the references themselves or on the general knowledge in the art, by which a skilled artisan would modify the references to include the missing subject matter. See *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1740-41, 82

USPQ2d 1385, 1396 (2007) (obviousness includes determining whether there was an apparent reason to combine known elements in the fashion claimed). With respect to the present claims, the references are devoid of any suggestion or appreciation of the benefits associated with melting the rotigotine and cement matrix (Claims 1 and 18), introducing rotigotine into a pre-melted cement matrix (Claim 20), or using a solvent-free process (Claims 18 and 20). In fact, the disclosure contributed by the Loper reference teaches away from melting the drug and instead provides the drug in solvent with the solvent removed by drying. The present rejection has failed to provide any basis for a skilled artisan to forgo such use of solvent or include the present melting or pre-melting processes, as required by *In re Kahn*, 441 F3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness."). In contradistinction, the present invention and claims provide and illustrate several advantages and benefits to overcome drawbacks of solvent-based systems. Specification page 1, line 26 to page 3, line 27. The combination of Chen, Metman, and Loper therefore cannot establish a case of obviousness.

In addition, Applicant reiterates that it is surprising that rotigotine lends itself to processing by the present hot-melt methods in that it remains stable under short-term heating to temperatures up to at least 160°C, and further, that it is released from matrices prepared in this way in a continuous fashion and at a therapeutically desirable rate (specification page 4, line 31 to page 5, line 4). Although rotigotine is known to be susceptible to oxidation, it remains stable after melting (as per the present claims) and is present in the resulting matrix at a purity level that is routinely better than 98% and generally over 99% (measured at 220 nm and 272 nm by HPLC; see specification page 5, lines 5-10; page 18, lines 23-27; and Tables 2, 3 and 4). The present compositions and methods protect rotigotine from critical environmental factors, such as light and oxygen, and can include higher rotigotine concentrations than are possible in compositions prepared by solvent-based processes; furthermore, the present invention provides improved safety and processing times (specification page 5, lines 11-17 and page 5, line 20 to page 6, line 21).

Independent Claims 1, 18 and 20, and all claims dependent directly or ultimately therefrom, are for reasons set forth above not obvious over the cited combination of

documents. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman and Loper is respectfully requested.

3. Rejection under 35 U.S.C. §103(a) over Chen in view of Metman, Loper and Noel

Claims 1–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Chen in view of Metman, Loper and U.S. Patent No. RE 36,754 ("Noel"). This rejection is respectfully traversed.

The combination of the Chen, Metman, Loper and Noel references cannot establish a *prima facie* case of obviousness for independent Claims 1, 18 and 20 since in each case the combination is missing one or more of the claimed features. The failure of a three-way combination of Chen, Metman and Loper to establish *prima facie* obviousness of the present claims is illustrated in the preceding section. Addition of Noel fails to cure these shortcomings, and, what is more, the Chen and Noel disclosures are incompatible and cannot be properly combined as no reason is provided as to how a skilled artisan would reconcile their disparate teachings. Likewise, Loper's contribution of "hot-melt deposition, extrusion and the like" employs solvent in contradistinction to express language (e.g., solvent-free) and resulting structure found in and produced by the present claims.

Details of the Noel reference are illustrated in Applicant's amendment filed December 22, 2008 and further illustrated below.

Chen in view of Metman, Loper and Noel, fails to teach or suggest a method, or product made by such method, in which rotigotine as active substance is dispersed and melted using the claimed hot-melt process. In particular, the combination of documents cited in the present rejection fails to teach or suggest infusing or dispersing any active substance, rotigotine or otherwise, wherein the active substance is melted. Thus, even if a skilled artisan attempted to combine the various disclosures of Chen, Metman, Loper and Noel (no admission is made herein that motivation would have existed for such combination), the combination would not provide all the features of the present claims.

The combination also fails to provide an apparent rationale by which a skilled artisan would modify the collective teachings to include the missing subject matter, and no reason based on the general knowledge in the art is identified by which a skilled artisan would be led to include the missing subject matter.

In addition, Chen's use of ropinirole dissolved in water or other solvent and mixed with a polymer to form a reservoir layer, and Loper's use of "hot melt deposition, extrusion and the like" to coat the drug, solvent, and reservoir matrix material, are at odds with Noel's preference for using a solvent-free composition and the benefits attributed by Noel to the hot-melt silicone PSA. It is not clear how a person of ordinary skill would reconcile these disparate teachings without contravening the operation of one of these references. Only the present specification and claims appreciate the surprising result that rotigotine remains stable in admixture with molten adhesive after the drug is melted (specification page 18, lines 23-27).

Independent Claims 1, 18 and 20, and all claims dependent directly or ultimately therefrom, are for reasons set forth above not obvious over the cited combination of documents. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman, Loper and Noel is respectfully requested.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.